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Editorial

Small Cell Lung Cancer and Prophylactic Cranial Irradiation (PCI): Perhaps the Question is Not who Needs PCI but who Wants PCI?

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WITH 175 000 new cases annually, lung cancer is the most frequent malignancy in adults in the European Community. Approximately 20% of these tumours are of the small cell subtype and roughly a third, chiefly when disease is confined to the thorax, will be in complete remission after aggressive induction therapy combining multidrug chemotherapy (CT) and thoracic radiation therapy. However, the majority of these patients will relapse and ultimately only 15–20% of complete responders will be long-term survivors (i.e. alive beyond 30 months). The major problems the physician is confronted with in these cases are how to preclude recurrences and how to cure them without generating unacceptable toxicity and without impairing the patient's quality of life.

The central nervous system (CNS) is one of the main organs invaded by small cell lung cancer (SCLC) and a frequent site of relapse. CNS metastases are found in up to 65% of patients at autopsy with the brain traditionally being considered a sanctuary for tumour cells [1]. Although the blood–brain barrier is supposed to bar the entry to harmful substances (in particular most cytotoxic agents) and thus protect the CNS, this shield does not function systematically since dramatic responses to CT have been achieved in brain metastases from SCLC and brain metastases also arise even when clear responses are being observed at all other sites [2].

Alternatively, the spectacular radiosensitivity of SCLC, which has been well established for decades, prompted the strategy of delivering prophylactic cranial irradiation (PCI) during induction treatment in order to prevent the development of metastases and their cohort of clinical symptoms. Several randomised trials were conducted in the 1970s [3]. Most of them concluded that PCI reduced the rate of brain metastases, but no clear gain was afforded for overall survival. Restrospective analyses of these studies suggest that any potential benefit would only be gained by patients in complete remission, a finding which is not at all surprising since they are the only ones likely to enjoy long-term survival and thus possibly benefit from adjuvant treatments. In the early 1980s, PCI was largely an integral part of the standard treatment of SCLC limited to the thorax with total doses usually ranging from 24 to 36 Gy. However, at the same time, it was incriminated in the emergence of adverse effects such as neuropsychological syndromes and brain abnormalities, detected perhaps because of the advent of more sophisticated imaging techniques such as computed tomography and magnetic resonance imaging. In any case, just how significant these changes were is hard to tell and could not be appreciated from an analysis of retrospective studies because investigators were unaware of the initial clinical status of patients who had received PCI and those who had not [4, 5]. Toxicity appeared to be more frequent and severe when PCI and CT were administered simultaneously, when PCI preceded CT containing radiosensitising cytotoxics, when the total RT dose exceeded 30 Gy or when fractions were above 3 Gy. Consequently, the systematic use of PCI was abandoned by some teams while others sought to deliver more cautiously administered PCI (total dose ≤ 30 Gy, fractions ≤ 3 Gy) to complete responders after induction therapy.

In 1985, the Institut Gustave Roussy designed an international randomised trial (PCI 85) to evaluate the effects of PCI on brain metastases and overall survival and to assess its toxicity in patients with SCLC in complete remission [6]. PCI was given at a dose of 24 Gy in eight fractions over 12 days. Exhaustive neuropsychological assessment was planned for patients submitted to PCI and for the control group at 6, 18, 30 and 48 months following treatment. 300 patients were enrolled and accrual was mainly limited to French centres. In 1988, a parallel trial was initiated focusing on the impact of PCI on overall survival. 211 patients were included in this second trial (PCI 88) up to 1994. Overall, 511 patients were finally included to investigate whether there was a survival benefit from PCI. The results of these studies have already been reported [7].

Similar questions were being addressed in the U.K. in a comparable trial, initiated in 1987, evaluating the frequency of brain metastases, toxicity and survival. In 1991, certain modifications were implemented to expand the accrual and the EORTC joined the study at that time. The results of this study, which included 314 patients up to 1995, are reported by Gregor and her colleagues in the present issue of the *European Journal of Cancer* (pp. 1752–1758). In this trial, all patients had SCLC confined to the thorax and were in complete

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remission after induction CT with a variety of regimens. Furthermore, 84% received thoracic radiotherapy. In the initial design, patients were to be allocated to either PCI delivering 36 Gy in 18 fractions or PCI delivering 24 Gy in 12 fractions or a control arm. The protocol had to be modified subsequently because of a slow accrual, and patients randomised to the PCI arm received a wide spectrum of doses ranging from 8 Gy in one fraction to 36 Gy in 18 fractions. In total, 194 received PCI and 120 were controls. Of this total population, 136 underwent extensive psychometric evaluation, two-thirds in the PCI arm and a third in the control arm; this proportion is equivalent to that of the initial randomisation. Based on the results of this study, the authors conclude that PCI significantly reduces the risk of brain metastases (from 54 to 30% at 2 years) without a statistically significant risk of radiation-induced brain damage, the latter conclusion being based on the numerous psychometric tests performed in these patients at 6 months and 1 year. The impact on the duration of survival was not significant, even though the mortality hazards ratio had been reduced by 14%.

Several reservations need to be expressed before integrating these results in current treatment strategies:

- The major advantage of the initial design, which planned to use two PCI schedules (24 Gy in 12 fractions or 36 Gy in 18 fractions), was to evaluate dose intensity. After 4 years, only 64 patients were included in this first part of the trial. The coordinators then decided to allow the radiotherapists to choose the dose and fractionation schedule to accelerate the accrual. Clearly such a procedure has led to an extremely heterogeneous study population in terms of treatment and thwarts any attempt at evaluating the impact of radiation doses and fractionation.
- Psychological assessment was one of the main objectives of the study since neurological toxicity is the main reason for limiting PCI. However, cognitive function was only assessed in 43% of patients and their quality of life and compliance to the tests were poor: only half of the patients were examined at the time of the planned assessments, namely at 6 months and 1 year of follow-up. Thus, only 16 and 12 cognitive function records were available at one year in the PCI and control group, respectively. Such numbers are far too limited to permit conclusive results.
- Finally, part of the toxicity associated with PCI will probably appear late in the day so that long-term follow-up will be required. The data available concern one year of follow-up and it is impossible to determine at this stage what toxic effects will be engendered at 3 and 5 years, that is, probably the time when the major symptoms attributed to PCI will be observed according to the retrospective studies which alerted clinicians to this problem.

Table 1. *Comparison of PCI* 85 *and UKCCCR/EORTC PCI*

	n		Brain metastases at 2 years		Overall survival at 2 years	
	PCI	Control	PCI	Control	PCI	Control
PCI 85 (IGR)	149	151	40%	67%	29%	21.5%
UKCCCR/ EORTC	194	120	30%	54%	25%	19%

Notwithstanding, the results of the UK/EORTC trial are consistent with those of the French trial (Table 1). They demonstrate that brain metastases can really be prevented and not simply delayed since a plateau is observed after 2 years in both studies. It is noteworthy that the most active induction CT regimens (i.e. those which contain etoposide combined with platinum compounds and/or an alkylating agent or an anthracycline) do not prevent a 60% risk of metastases to the brain, the first site of relapse in 45% of cases at 2 years in PCI85. PCI did not prevent brain metastases in a third of cases at 2 years. Could such inefficiency be related to the size of the micrometastases which were not detected at the time of PCI?

No striking early toxicity was noted with PCI and no major neurological symptoms have been observed after 2–3 years of follow-up. Nevertheless, a longer follow-up is needed for a better appreciation of brain toxicity due to PCI in long-term survivors cured of SCLC.

The impact of PCI on the survival of patients in complete remission is probably modest. The relative risk of death was comparable in the UK/EORTC trial and in the two Institut Gustave Roussy trials, 0.83 and 0.86, respectively. This gain is comparable to that acquired with thoracic radiation in patients with limited SCLC [8]. The on-going meta-analysis of all available randomised trials will better clarify the extent of the benefit for survival, if any.

Given the above observations, we suggest that clinicians strive to prevent the emergence of brain metastases since the cost/benefit ratio, in terms of quality of life, appears to be in favour of PCI. This attitude is reinforced by the fact that, in PCI85, survival was poor after the occurrence of brain metastases, regardless of the treatment group and in spite of full-dose radiation used for salvage treatment. In any case, it is the physician's duty to inform the patient clearly and consider his/her quality of life as a determining factor in his choice of treatment.

Finally, there is still tremendous room for improvement and many unresolved questions await investigation in prospective randomised trials:

- None of these studies provide clear-cut information on the optimal dose of radiotherapy. Higher doses probably ensure better prevention, but a greater risk of toxicity. Seemingly, 30 Gy in 18 fractions are acceptable but on no account should they be delivered concurrently with CT.
- No data offer guidelines on the ideal timing of PCI. Is it better to deliver it early, at the same time as thoracic radiation (generally delivered early in most newly designed programmes) or later, after the complete course of induction treatment and when complete response is well established and confirmed?
- Is there an age after which PCI-induced toxicity overshadows the benefit because of microscopic damage to vessels?

In any case, on both sides of the Channel, comparable studies have generated similar results and this should kindle the flame of intensified future cooperation.

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